Remarks

The foregoing amendments in the claims are fully supported by the specification and claims as originally filed. New claim 37 includes the subject matter of original claim 20 and its antecedent, claim 1. New claim 38 includes the subject matter of original claim 29 and its antecedents, claims 1, 26, and 28. New claims 39-42 include the subject matter of original claims 31 and 32 as applied to new claims 37 and 38. No new matter is added by the new claims. All amendments have been made solely to facilitate the prosecution of the present application, and without acquiescence in any of the rejections and without prejudice to future prosecution of canceled subject matter in this or in continuation or divisional cases.

Claims 1, 20, 25, 26, 28, 29, 31-36 were pending in the application, with claims 1, 25, 26, 28, and 31-36 rejected, claim 29 objected to, and claim 20 withdrawn by the Examiner as being drawn to a non-elected species. With the present amendment, claims 1, 25, 26, 28, and 31-36 remain pending, claims 20 and 29 have been cancelled and new claims 37-42 have been added.

Claims 1, 25, 31-33 and 36 have been rejected under U.S.C. § 103(a), allegedly as being obvious over Zapata et al. (FASEB J. 1995, Abstract #1288, 9:A1479, IDS #98) in view of Braxton (US Pat. No. 5,766,897IDS #98). Claims 26 and 28 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata *et al.* in view of Braxton *et al.*, as applied to claims 1, 25, 31-33 and 33 and 36 above, and further in view of Doerschuk *et al.* (U.S. Patent 5,702,946, IDS #18). Claims 34 and 35 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata *et al.* in view of Braxton *et al.*, and in further view of Griffiths *et al.* (US Patent No. 5,670,132, IDS #13). Applicants traverse the rejections as discussed below.

The Withdrawal of Rejections to Claims 1, 25-26, 28-29, and 31-36

Applicants note, per the Office communication mailed September 30, 2003, the withdrawal of the rejections to claims 1, 25-26, 28-29, and 31-36 under 35 U.S.C. § 112, 2nd paragraph; the withdrawal of the rejections to claims 1, 25-26, 28-29, and 31-36 based upon either U. S. Patent 6,133,426 or U.S. Patent 6,025,158; and the withdrawal of the provisional rejections to claims 1, 25-26, 28-29, and 31-36 under the judicially created doctrine of obviousness-type double patenting.

The Subject Matter of Original Claim 20, now Claim 37

Applicants reiterate the arguments presented in the Amendment and Response mailed on July 23, 2003 directed to the withdrawal by the Examiner of Claim 20 from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species. In that response, Applicants traversed the withdrawal of Claim 20. In the present amendment, claim 20 stands cancelled, with the subject matter of claim 20 included in independent claim 37 which incorporates the subject matter of claim 20 and of its parent, claim 1.

Claim 1 was within the group of claims directed to the subject matter elected for prosecution pursuant to the Restriction Requirement. Claim 37 recites the same limitations as claim 1, except that it is further limited to conjugates including a PEG that "has an average molecular weight of at least about 40 kD." A PEG molecule having an average molecular weight of at least 40 kDa would qualify as being a member of a genus of PEG molecules having an average molecular weight of at least 20 kD recited in Claim 1. Thus, claim 37 is within the species elected for prosecution in this case.

Applicants further submit that claim 37 is free of, and is not obvious over, the prior art. The Examiner states (point 14, page 6, paper No. 14) "Zapata et al. teach a conjugate consisting essentially of a humanized anti-CD18 Fab' fragment covalently coupled via sulfhydryl group in the hinge region to a single chain of a PEG molecule (MePEG) that is either 5 kD or 10 kD." However, Zapata provides no suggestion of a

PEG molecule having an average molecular weight of at least 40 kDa, nor does Zapata provide any motivation to combine with any other reference to provide a PEG molecule having an average molecular weight of at least 40 kDa. Similarly, Braxton fails to teach or suggest a PEG molecule having an average molecular weight of at least 40 kDa. The Examiner states (point 14, page 7, fifth paragraph, lines 3-4, paper No. 14) "the identification by Braxton of 20 kD as being the upper end of the molecular weight range of PEGs taught." Thus, identifying an upper limit below the minimum average molecular weight recited in claim 37, Braxton teaches away from the invention of claim 37.

Claim 37 being properly drawn to subject matter within the elected subject matter of the present application, and being novel and not obvious in view of the cited references, applicants respectfully request the consideration and allowance of claim 37 and its dependent claims, Claims 39 and 40.

The Objection to Claim 29

Claim 29 was objected to in the Office Communication dated September 30, 2003. Claim 29 stands cancelled in this amendment. However, new claim 38 recites the subject matter of claim 29 and all limitations of the preceding claims from which claim 29 depended, claims 1, 26 and 28. Applicants believe that independent claim 38, reciting the subject matter of claim 29 and its antecedent claims, overcomes the objection to claim 29. Applicants note that claim 38 recites a PEGylated humanized anti-human-IL-8 antibody Fab' fragment having a novel complementarity determining region. Accordingly, applicants respectfully submit that claim 38 and its dependent claims 41 and 42 (which are further limiting by adding an additional element to claim 38) are free of the prior art, not obvious, and stand in allowable form.

The Rejections of Claims 1, 25, 31-33 and 36 under 35 U.S.C. § 103(a)

Claims 1, 25, 31-33 and 36 have been rejected under U.S.C. § 103(a), allegedly as being obvious over Zapata et al. (FASEB J. 1995, Abstract #1288, 9:A1479, IDS

#98) in view of Braxton (US Pat. No. 5,766,897IDS #98). Although none of the cited references teach antibody fragments PEGylated with PEG having an average molecular weight of at least 20 kD, the Examiner states "it would have been obvious to one of ordinary skill in the art to use higher molecular weight PEGs for covalent linkage to any Fab' antibody fragment for which one desired to reduce the serum clearance rate" (point 14, page 7, first paragraph, paper No. 14).

In the interest of brevity, applicants will not merely repeat previously presented arguments. However, applicants maintain and reiterate arguments presented in the responses mailed July 23, 2003 and on December 30, 2002, all of which arguments are incorporated by reference herein.

In order to establish a prima facie case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claims 1 and 36 recite a conjugate including the elements "an antibody Fab' fragment," a "covalently attached PEG molecule having an average molecular weight of at least 20 kD," the conjugate having an apparent size that is "at least about 500 kD," and that is "at least about 8 fold greater than the apparent size of the antibody fragment." Dependent claims 25 and 31-33 also include all these elements.

As discussed previously, no cited reference teaches a PEG molecule having an average molecular weight of 20 kD or more (as noted above, Braxton teaches that 20 kD is an upper limit). No cited reference teaches or suggests a conjugate having an

apparent size that is "at least about 500 kD." Moreover, no cited reference teaches an antibody-PEG conjugate that is "at least about 8 fold greater than the apparent size of the antibody fragment."

As noted by the Examiner, "the references are silent with respect to the apparent size of the conjugate and the relationship of the apparent size of the conjugate to that of the unconjugated Fab' fragment" (page 7, line 37-39, paper 14). However, the Examiner states "motivation to select a 20 kD PEG would necessarily result in these properties without any appreciation of them by the ordinary artisan" (page 7, line 44-45, paper 14).

Applicants agree that, absent the disclosure of the present invention, the ordinary artisan would not appreciate the properties of the present invention. Applicants respectfully note that without appreciation of the elements of the claimed invention by an ordinary artisan, the invention is not obvious over the prior art.

Under 35 U.S.C. § 103, the claimed invention must be considered as a whole: "treating the advantage as the invention disregards statutory requirement that the invention be viewed 'as a whole'" (*Jones v. Hardy*, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1984); see also, e.g., *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), and that motivation to combine must come from the prior art references and not as a result of hindsight. *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999). "[A] retrospective view of inherency is not substitute for some teaching or suggestion supporting an obviousness rejection." *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993).

Applicants respectfully note that the cited references not only fail to teach all the elements of the claimed invention, they fail to provide motivation or suggestion to combine to provide the claimed invention, and fail to provide any reasonable expectation of success were such a combination to be made.

The Zapata abstract does not use the words "apparent size" nor does it teach or suggest that the "apparent size" of a conjugate might be at least about 500 kD and at least 8 fold greater than the size of the antibody fragment. A search of the Braxton patent failed to find the word "size" and fails to find a discussion of the apparent size of a conjugate being greater than the apparent size of the antibody fragment. Thus, Braxton also fails to teach or suggest that the "apparent size" of a conjugate might be at least about 500 kD and at least 8 fold greater than the apparent size of the antibody fragment. Thus, each cited reference lacking disclosure of at least this element, the references, even if combined, fail to make obvious the claimed invention.

Furthermore, there is nothing in the cited references to lead one of ordinary skill in the art to expect that conjugation of a PEG molecule of at least 20 kD to an antibody fragment would provide a conjugate having an apparent size that is at least about 500 kD. Moreover, there is nothing in the cited references to lead one of ordinary skill in the art to expect that conjugation of a PEG molecule of at least 20 kD to an antibody fragment would provide a conjugate having an apparent size that is at least about 8 fold greater than the apparent size of the antibody fragment. Thus, the cited references also fail to provide suggestion or motivation to provide this element of the claimed invention. Lacking such motivation or suggestion, there is no motivation in the references to combine them.

Each reference lacking any teaching or suggestion that the apparent size of an antibody fragment-PEG conjugate may be greater than about 500 kD and at least 8 fold greater than the apparent size of the antibody fragment, the cited references provide no reasonable expectation of success for such a combination.

Accordingly, since the cited references do not disclose a conjugate of an antibody fragment conjugated with a PEG molecule of at least about 20 kD having an apparent size of at least about 500 kD and do not disclose conjugate of an antibody

fragment conjugated with a PEG molecule of at least about 20 kD having an apparent size of at least about 8 fold greater than the apparent size of the antibody fragment; since the cited references provide no motivation to be combined to provide such a conjugate; and do not provide any reasonable expectation of success were the references to be so combined, applicants respectfully submit that claims 1, 25, 31-33 and 36 are not made obvious by the cited references. Accordingly, applicants submit that the rejections of claims 1, 25, 31-33 and 36 under 35 U.S.C. § 103 are overcome.

The Rejections of Claims 26 and 28 under 35 U.S.C. § 103(a)

Claims 26 and 28 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata *et al.* in view of Braxton *et al.*, as applied to claims 1, 25, 31-33 and 33 and 36 above, and further in view of Doerschuk *et al.* (U.S. Patent 5,702,946, IDS #18). Zapata *et al.* and Braxton *et al.* were cited as discussed above, Doerschuk *et al.* was cited for its disclosure of anti-IL-8 antibodies, their humanized Fab' fragments, and other disclosure related to anti-IL-8 antibodies.

As discussed in response to the previous rejection, the combination of Zapata *et al.* and Braxton *et al.* does not make obvious the claims on which Claims 26 and 28 depend. Doerschuk *et al.* likewise fails to disclose or suggest a conjugate of an antibody fragment conjugated with a PEG molecule of at least about 20 kD having an apparent size of at least about 500 kD and an apparent size of at least about 8 fold greater than the apparent size of the antibody fragment. Accordingly, Doerschuk *et al.* does not make up for the deficiencies of the primary combination, Claims 26 and 28 are not obvious for the same reasons as the base claims on which they depend. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

The Rejections of Claims 34 and 35 under 35 U.S.C. § 103(a)

Claims 34 and 35 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zapata *et al.* in view of Braxton *et al.*, and in further view of Griffiths *et al.* (US

Patent No. 5,670,132, IDS #13). Zapata *et al.* and Braxton *et al.* were cited as discussed above, Griffith *et al.* was cited for teaching the radiolabeling of a Fab'-PEG conjugate. However, Griffith *et al.* fails to disclose or suggest a conjugate of an antibody fragment conjugated with a PEG molecule of at least about 20 kD having an apparent size of at least about 500 kD, and having an apparent size of at least about 8 fold greater than the apparent size of the antibody fragment. Since Griffith *et al.* does not make up for the deficiencies of the primary combination, Claims 34 and 35 are not obvious for the same reasons as the base claims on which they depend. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

CONCLUSION

Applicants believe that all pending claims pending are in condition for allowance. Accordingly, reconsideration and allowance of all claims is respectfully solicited.

Please charge any fees, including any additional fees for extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39766-0093C1**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: December 22, 2003

By: _____
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